Small Intestinal Bacterial Overgrowth in Chronic Pancreatitis

A dissertation submitted in partial fulfilment of the requirements for DM (Branch IV, Gastroenterology) examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai to be held in August 2013.

Certificate

This is to certify that this dissertation entitled **"SMALL INTESTINAL BACTERIAL OVERGROWTH IN CHRONIC PANCREATITIS"** is a bonafide work done by Dr.Kapil Dev Jamwal in partial fulfilment of the rules and regulations for DM (Branch IV – Gastroenterology) examination of The Tamil Nadu Dr MGR Medical University, to be held in August 2013.

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Date:

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KAPIL DEV JAMWAL

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INTRODUCTION

The human small intestine is the site of digestion and absorption of major macro and micronutrients. Any abnormality which affects this part of bowel may lead to nutritional deficiencies as well as malabsorption syndrome. An important cause of malabsorption syndrome is Small Intestinal bacterial Overgrowth (SIBO). [1,2,3,4]

The bacterial count is extremely low in the stomach and small intestine. The normal count in stomach is 10^2-10^3 CFU/ml, in duodenum is 10^3 CFU/ml, in jejunum the count is < 10^4 CFU/ml and in ileum it's upto 10^7-10^9 CFU/ml.

SIBO (small intestinal bacterial overgrowth) is defined as increased bacterial counts in the proximal small bowel (jejunum and ileum). It is also defined as the replacement of normal small bowel bacteria with the colonic bacteria. SIBO is diagnosed by jejunal aspiration (gold standard) and various breath tests (Hydrogen breath tests, C^{14} breath tests, lactulose breath tests, methane breath tests etc.)[5,6] The clinical manifestations of SIBO may range from asymptomatic stage to malabsorption syndrome.

Chronic pancreatitis has been defined as a clinical condition associated with morphological (fibrosis/calcification) of pancreas and/ or functional (exocrine and endocrine) insufficiency of the pancreas. [7,8] SIBO has been reported in chronic pancreatitis and may be due to drugs (Proton pump inhibitors / analgesics), deficiency of pancreatic enzymes, impaired small bowel motility or surgery. [13]

The literature regarding SIBO in chronic pancreatitis is meagre and conflicting, with the recent literature contemplating that SIBO is uncommon in Chronic pancreatitis.[9,10,14] Conflicting reports on prevalence of SIBO could be attributed to absence of population based prevalence studies as well as non utilization of gold standard (jejunal aspirate culture) for diagnosing SIBO.

AIMS

1. To determine the frequency of SIBO (Small intestinal bacterial overgrowth) in chronic pancreatitis.

2. To evaluate the sensitivity and specificity of GHBT (Glucose Hydrogen Breath Test) in SIBO (Small intestinal bacterial overgrowth) by comparing it to jejunal aspirate culture (Gold standard).

MATERIAL AND METHODS

Study Design:

Observational, cross-sectional, prospective and a pilot study.

Setting

- Tertiary care centre in South India with a total bed intake of 2400 patients.
- Patients were recruited from Gastroenterology OPD and Pancreatic Biliary clinic.
- The duration of the study was from August 2011 to December 2012.
- The study was approved by the Institutional Ethics and Research Review Board.

Inclusion Criteria:

1. Adults between the ages of 18 – 60 years.
2. Diagnosed as Chronic Pancreatitis, criteria defined as later.

Exclusion criteria

1. Age < 18 years and > 60 years
2. Patients who had received any antibiotics in last 3 months.
3. Patients who were on PPI's (proton pump inhibitors) over the last 2 weeks.
4. Patients who were on pancreatic supplements for at least 2 weeks before recruitment.

5. Patients who underwent any upper abdominal surgery including a pancreatic or gastric surgery.
6. Patients who had any radiation to the small bowel.
7. Patients with upper GI malignancies.
8. Patients with diverticulosis of the small bowel.
9. Pregnancy
10. Patients who refused to give a valid consent.

Diagnosis of chronic pancreatitis:

Chronic pancreatitis was diagnosed on basis of history which was suggestive of pancreatic pain supported by laboratory parameters as well as radiological imaging (USG abdomen, CECT abdomen, MRCP or EUS). The radiological parameters on USG abdomen, CECT abdomen, MRCP diagnostic of chronic pancreatitis were dilated pancreatic ducts (major or minor), pancreatic calcifications (ductal or parenchymal), atrophy or enlargement of the gland, irregular gland margins, changes in the parenchymal echotexture. The EUS criteria diagnostic of chronic pancreatitis (parenchymal and ductal) were also used for the diagnosis.

After recruiting the patient for the study, a detailed history was taken regarding total duration of symptoms of dyspepsia, pain abdomen and symptoms to suggest diabetes or steatorrhoea. The

duration of each symptom was recorded in detail. The socio economic status was recorded according to the modified Kuppuswamy scale.[15]

All patients had the following investigations done as per protocol for chronic pancreatitis at our centre – tests to determine etiology of chronic pancreatitis, endocrine dysfunction (blood sugars), exocrine dysfunction (72 hour stool fat) and nutritional status (BMI, Total protein/ albumin, Vitamin B_{12}, folic acid). Imaging studies – USG abdomen, CECT abdomen, MRCP or EUS were also performed.

Determination of Small Intestinal Bacterial Overgrowth

a. Jejunal aspirate culture

b.. Glucose Hydrogen breath Test

Jejunal aspirate culture

Method of jejunal aspiration

Requirements:

A. Endoscope – Olympus GIF 150 series (manufactured at Japan), a paediatric colonoscope Olympus PCF 150 series.

B. A sheathed tube specially designed for this study- A Wilson Cook sclerotherapy needle was converted into aspiration needle after it's needle tip and outer tube were cut at it's distal end, the outer tube being at least 2 cm shorter than it's inner tube.

C. Culture tubes and culture media for aerobic and anaerobic bacterial culture.

Technique for Obtaining Jejunal Juice for Culture:

1. After an overnight fast, the patients underwent jejunal intubation using an endoscope. Topical Anaesthesia was applied prior to the procedure. Initially a paediatric colonscope was used. The endoscope was advanced to at least 10 cm beyond the DJ flexure and the position confirmed by fluoroscopy. When the scopist was confident of reaching jejunum with a gastroscope, jejunal intubation was performed with a gastroscope. For initial intubation of the jejunum, the patients were sedated with midazolam. But later on it was stopped, as the patients experienced more discomfort in the post procedure period

2. After intubating the jejunum (at least 10cm beyond the DJ flexure), a specially designed sheathed tube for aspiration was introduced (Modified sclerotherapy needle, Cook medical). The tip of the needle was cut and the outer sheath was cut at least 2-3 cms shorter than the inner tube. A rubber stooper was placed at the tip of the outer tube after washing and was in the same position during sterilization. This was to prevent contamination of the inner tube when passed through the biopsy channel of the endoscope (Figure 1).

3. After the tube was introduced into the jejunum, through the endoscope biopsy channel, the rubber stopper at the tip of the outer tube was dislodged when the inner tube being pushed out (Figure 3).

4. A EUS (endoscopic ultrasound) suction needle was used to aspirate the jejunal contents .The endoscopist, the assisting nurse and the technician used strict aseptic precautions while obtaining the sample. As soon as 2-3 ml of jejunal juice was aspirated into the sterile syringe, the inner tube was withdrawn into outer tube and the endoscope was withdrawn with the tube in situ (Figure 2)

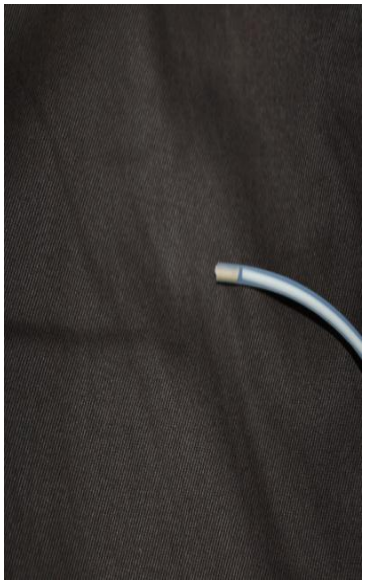
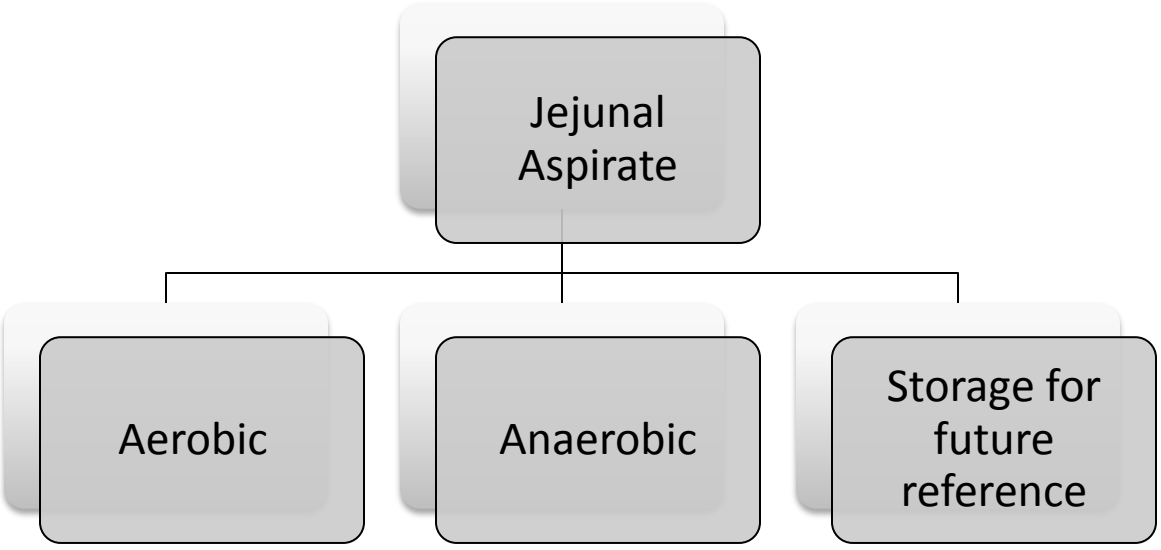


Figure 1: Tube with rubber stopper at the tip

Figure 2: Base of the tube

Figure3: Rubber dislodged with the inner tip out

5. The aspirate was then divided into 3 portions and sent for aerobic culture, anaerobic culture and a third portion stored for future reference.



Culture technique:

1. 50µL of the diluted (all four serial dilutions) and non-diluted samples was spread on the corresponding aerobic and anaerobic media plates.
2. Aerobic culture media used were – MacConkey's media, Nutrient agar, Salmonella Shigella agar (SS agar) and Blood agar; the diluted sample was plated on all these media for 24 hours at 37 ˚c.
3. The anaerobic media used were – Gut microbial medium, MRS agar and Bifidobacterium agar at 37 ˚C for 24 -48 hours in 80% nitrogen and 20% carbon dioxide (CO_2).

4. The culture media were first observed after 24 hours of incubation for any growth followed by every 12 hourly thereafter to look for colonies and further dilutions if required.
5. Dilutions from 10^{-1} to 10^{-4} were generally performed. After a 24- to 48 h incubation at 37˚C, colonies were counted. The choice of the last dilution was decided after the results of direct examination.

A CFU (colony forming unit) of > 10^5 /ml was diagnosed as SIBO.

Glucose Hydrogen Breath Test (GHBT)

Principle and technique:

The source of hydrogen in humans is the metabolism of carbohydrates by the native bacteria in the large intestine. In patients with SIBO, glucose that reaches the jejunum is metabolized by the bacteria in the proximal small bowel. The metabolized glucose produces hydrogen which diffuses into the systemic circulation, and about 20% of the hydrogen gas produced is expired from the lungs into the air.[16]

In GHBT, glucose is consumed by the patient at a predefined dose depending upon body weight of patient with a minimum of 50 gram to a maximum of 75 gram. The air is expired by the patient is collected via a mouth piece which is then connected to hydrogen breath meter (manufacturer Bedfont, UK). The machine detects the breath hydrogen and expresses the results in parts per million (ppm) of hydrogen in the expired air. In normal individuals the expired air contains hydrogen levels of < 20 ppm in fasting state and the rise after glucose is not more than 12 ppm above the baseline.

Positive test: Baseline breath hydrogen level above 20 ppm or a peak in breath hydrogen level after glucose which is 12 ppm above the baseline level.

Precautions:

1. The patients should be fasting overnight.

2. The patients should avoid smoking.

3. The patients should not exercise prior to the test.

4. The patients should avoid fermentative diets (high fiber diet), atleast the night prior to the breath test.

Method:

a. After an overnight fast, the patient was asked to do a mouth gargle with chlorhexidine followed by a baseline expired breath, which was recorded as baseline or zero minute.

b. Then patient was given 50 gm / 75 gm of glucose dissolved in fresh water (250 ml).

c. Then the patient was instructed to given breath samples every 20 min till 120 minutes.

d. The results were recorded and plotted on a graph and report given as negative GHBT or Positive GHBT (Figure 4).

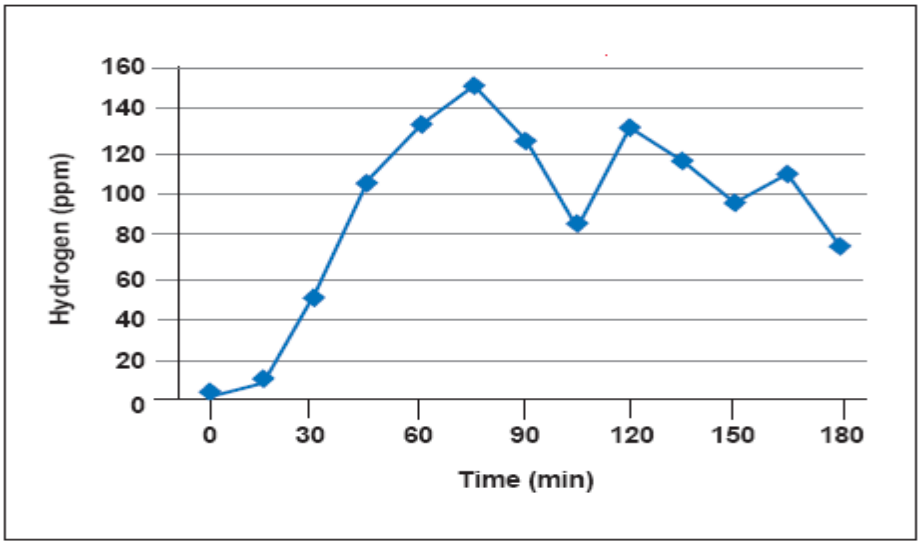


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Figure 4: Positive glucose hydrogen breath test

STATISTICAL METHODS

The categorical data were compared using the Fisher exact test.

The continuous data were compared using Mann Whitney U test as the data did not have normal distribution.

The SPSS 16 version of the software was used to calculate the data.

As the study was a pilot study, all patients who were diagnosed with chronic pancreatitis and fulfilled the inclusion and the exclusion criteria were recruited. Since there were limited finances, the study could not be changed into a prevalence study and was continued as a pilot study.

REVIEW OF LITERATURE

Introduction

SIBO (small intestinal bacterial overgrowth) is characterized by excessive growth of bacteria in the small intestine especially in the proximal small bowel. Characteristically the normal flora of the proximal small bowel is gram positive aerobes but in SIBO it is gradually replaced by gram negative aerobes and anaerobes.[16] In the tropics, the normal small bowel flora has been defined from $10^5 – 10^7$ CFU's/ml in jejunal fluid. The recent literature has shown that bacterial CFU's of 10^5 /ml can also be accepted for the diagnosis of SIBO. [17,18]

The prevalence of SIBO (small intestinal bacterial overgrowth) in a normal healthy adult population is difficult to be defined as there is lack of data in the literature and non utilization of the gold standard for this purpose in the studies. There have been multiple studies which have utilized breath tests for the prevalence of SIBO in the normal population and among them SIBO (small intestinal bacterial overgrowth) ranges from 0 to 13 % when GHBT (glucose hydrogen breath test) was utilized as compared to LHBT (lactulose hydrogen breath test) which demonstrated a prevalence of 21% in the general population and when ^{14}C-d xylose was used it showed an overall prevalence of 0-35% of SIBO in the normal study population.[19]

There are multiple etiologies of SIBO, as shown in table 1 :

TABLE 1: ETIOLOGY OF SIBO

Physiological	Old age,[23,24] Achlorhydria[25,26]
Small intestine stasis 1.Abnormal motility 2. Diverticulosis[36]	1.1 Neuropathy including Diabetes mellitus.[27,28,29] 1.2 Scleroderma[30] 1.3 Amyloidosis 1.4 Hypothyroidism 1.5 Idiopathic intestinal Pseudoobstruction[31,32] 1.6 Radiation[33,34] 1.7 IBD especially Crohn's disease[35]
Post surgical[37,38]	Gastrojejunostomy, Pancreatic resection & IC valve resection Strictures (Crohn's disease, radiation and surgery).
Intestinal Fistulas	Gastrocolic Small bowel fistulas due to multiple etiologies
Multifactorial	1. CLD (chronic liver disease)[39,40,41] 2. IBS (irritable bowel syndrome)[42,43,44] 3. Celiac disease[45,46]

	4. Chronic pancreatitis14 5. Immune deficiency syndromes including HIV[47,48] 6. CKD (chronic kidney disease) 7. Tropical sprue[17,49] 8. Rare: Farsenoid receptor alterations[50]

Pathogenesis of SIBO:

The development of SIBO is seen due to multiple etiologies and their interactions, but when taken into isolation two factors which contribute more than other factors are a. altered small intestinal motility and b. decreased gastric acid production.

The protective factors which play role in prevention of SIBO (small intestinal bacterial overgrowth) are:

i. Protective mucus lining of the small bowel mucosa.

ii. Various enzymes in the secretions (pancreatic, biliary and intestinal) which are present in the intestinal lumen.

iii. Commensal flora which plays a protective role for e.g Lactobacilli, Bifidobacteria.

iv. Intact IC (ileocecal) valve.[52,53]

The anaerobic bacteria which are predominant in SIBO lead to a state of nutritional deficiency by utilizing cobalamin which in turn leads to decreased levels of vitamin B_{12}, which may lead to various clinical manifestations ranging from asymptomatic macrocytic anemia to neuropathy and subacute degeneration of the spinal cord. [54] There is associated malabsorption of fat soluble vitamins except vitamin K which is produced in excess by the overgrowing bacteria. At the microscopic level there is alteration in the brush border enzymes and which may further add to malabsorption syndrome.[55]

There are morphological and functional alterations in the small intestinal mucosa in chronic pancreatitis. There can be enteritis with loss of mucosal enzyme activity which may lead to decreased absorption, decreased local immunity and bacterial overgrowth. [56]

Methods of diagnosis of SIBO:

The gold standard for diagnosis of SIBO (small intestinal bacterial overgrowth) is jejunal aspiration. Bhat and colleagues defined a CFU of 10^7/ ml as normal in tropics.[17]

There are multiple techniques of diagnosis of SIBO (small intestinal bacterial overgrowth) and these can be divided in two types:

a. Invasive and

b. Non invasive.

Invasive includes: Jejunal aspiration methods such as

1. Fluoroscopic intubation of the jejunum.[20,21,22]

2. Endoscopic mucosal brushings[57]

3. Endoscopic mucosal biopsies.[58,59]

4. Endoscopic jejunal aspiration.[21]

There are various drawbacks of this techniques are:

1. These are invasive methods.
2. There are high chances of contamination of the aspirate with oro pharyngeal or gastric or duodenal secretions.
3. The culture based techniques have certain limitations in addition to being invasive, which are
    (i) Low reproducibility – multiple studies have shown that the cultures have diagnostic yield of < 40%.[60]
    (ii) The period of incubation and final results are obtained may take 48 hours to few days.

A recent study done by Chandra et al showed that endoscopic biopsy culture may be as good as jejunal aspirate in Indian population.[59] The study population included 48 pairs of fluid and mucosal biopsies, in 45 pairs they were able to obtain both jejunal biopsy and as well as jejunal fluid. The study concluded that the jejunal mucosal biopsy can be used as an alternative to jejunal aspiration for assessing jejunal microflora.

Non invasive methods include:

a. Breath tests

b. Radiological methods including a 1H-NMR spectroscopy- 41 and various imaging techniques of the small bowel.

Breath Tests:

The breath tests came into existence due to drawbacks of the jejunal aspirate as described earlier. These are indirect ways of estimating SIBO (small intestinal bacterial overgrowth) by means of estimating level of certain end products of substrates in the expired air produced by metabolism by small bowel or large bowel bacteria.

Principle of breath tests: The source of hydrogen in humans is the metabolism of carbohydrates by the native bacteria. These complex and simple carbohydrate metabolism and absorption is deficient in a group of patients and this leads to development of malabsorption. When this

associated with proximal migration of the colonic bacteria into the small bowel or there is overgrowth of native bacteria, this leads to SIBO (small intestinal bacterial overgrowth).

This hydrogen which is produced after the metabolism is very quickly absorbed into the blood and is expired in the air. This can be easily picked up and measured in the expired air utilizing the breath tests.

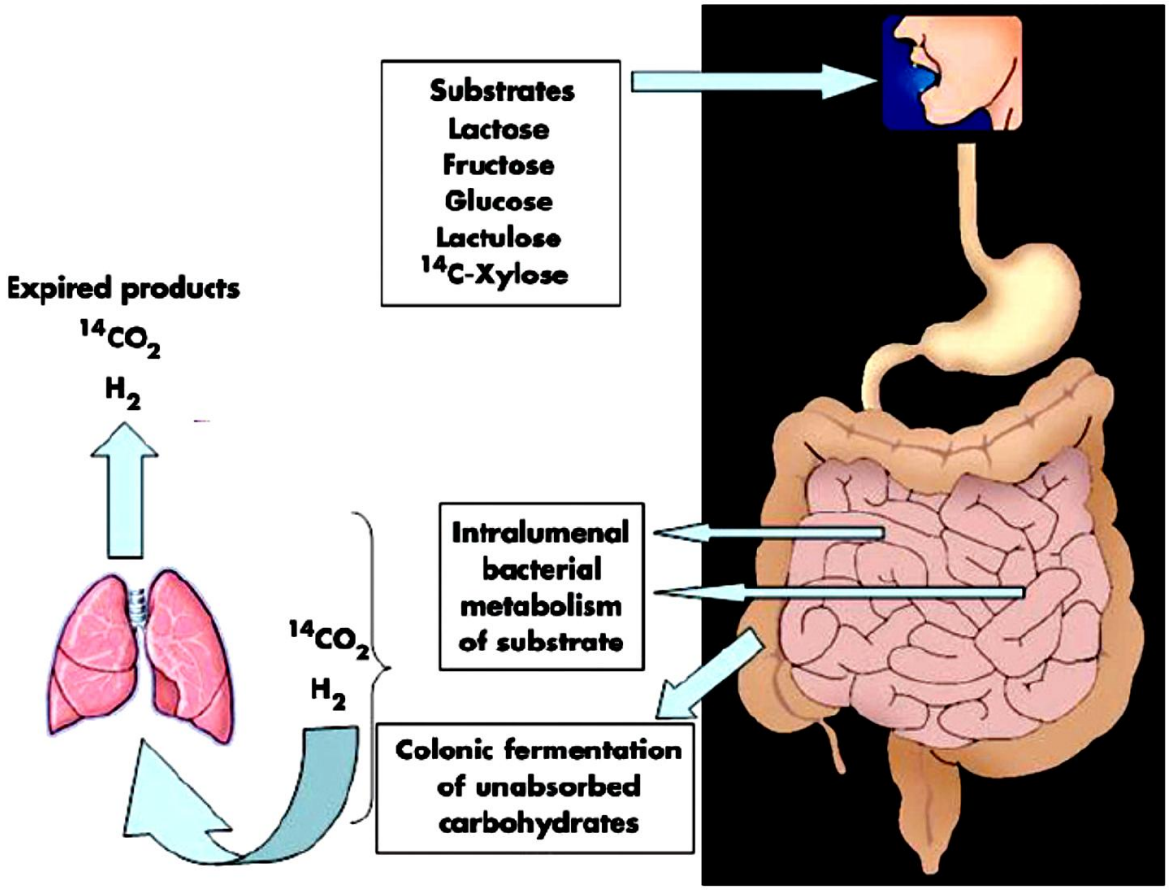


Figure 5

There are various types of breath tests and there sensitivity and specificity ranges from 30-80% and 50-95% respectively.[61,62]

TABLE 2: TYPES OF BREATH TESTS WITH THEIR SENSITIVITIES AND SPECIFICITY

Test / reference	Sensitivity (%)	Specificity (%)
Glucose Hydrogen breath Test		
Kalin and Wang (1988)[63]	93	78
Corraza etal (1990)[64]	62	83
Ghoshal et al (2006)[65]	44	80
Lactulose hydrogen Breath tests		
Ghoshal et al (2006)[65]	31	86
Rhodes et al (1979)[66]	89	100
D Xylose		
King and Toskes (1986)[67]	95	100
Lewis et al (1999)[68]	79	85
C14 – Bile acid breath test		
King et al (1980)[69]	33.3	-

Advantages of breath tests:

1. Simple to perform
2. Cheap
3. Easily available
4. Non invasive
5. Does not require specially trained staff.
6. Results are available at the end of the test.

Disadvantages of the breath test:

1. Low sensitivity
2. In the general population about 15 % patients are methane producers and these patients will not be diagnosed with conventionally used Hydrogen breath tests.[70]
3. The results depend upon the patient related factors which includes smoking, consumption of high fiber prior to the test, exercise during the test etc.
4. The slow and rapid transit of the small bowel may alter the interpretation of the results.

The other types of the breath tests:

1. Lactulose hydrogen breath test
2. Lactose hydrogen breath tests

3. Rice breath test
4. C^{14} D xylose breath test
5. Cholyl – PABA test
6. Methane breath test
7. ^{14}C-Glycocholic acid breath test

Lactulose Hydrogen breath test: The principle of the glucose and lactulose hydrogen breath test is similar, in this test a non absorbable starch that is metabolized in colon by the action of the colonic bacteria and it produces a late peak in the breath analysis.[71] It has been utilized in estimating OCTT (oro cecal transit time).

Lactose Hydrogen breath test: It detects lactose malabsorption and it is shown in previous study by Reis et al in 1999 that the children who had Lactose malabsorption had no statistical relationship with SIBO (small intestinal bacterial overgrowth) and it was noted in 7.2% children.[72]

^{14}C-xylose and ^{13}C-xylose breath tests: These tests detect a labeled CO_2 that is produced by the metabolism of a labeled substrate in the proximal small bowel with the action of bacteria. The substrate used is d-xylose and labeled carbon is either C-13 or C-14. A study was done in 2000 by Stotzer et al, which compared radio labeled d-xylose with glucose hydrogen breath test and

found that and found that the sensitivity of the GHBT was 58% with a specificity of 86% respectively.[73,74]

Cholyl PABA: It has been described in literature but it is not able to distinguish between SIBO and malabsorption.

^{14}C-glycocholic acid breath test: It is one of the earliest used breath test in SIBO. It is not used these days due to it's low specificity and sensitivity and unable to distinguish between SIBO and malabsorption.[75]

1H-NMR spectroscopy for SIBO (small intestinal bacterial overgrowth): A study was done in 2006 in India which used the proximal small bowel aspirate of patients with malabsorption syndrome who had SIBO (small intestinal bacterial overgrowth) and who did not had SIBO (small intestinal bacterial overgrowth). The aspirate was analyzed using a spectrometer (NMR). The study showed that the patients with SIBO (small intestinal bacterial overgrowth) had increased quantities of bile acid, cholesterol, lactate and acetate in their intestinal aspirate. The acetate had a statistical positive correlation with SIBO (small intestinal bacterial overgrowth).[76]

Chronic pancreatitis:

Definition – Chronic pancreatitis is a clinical condition associated with fibrosis and calcification of pancreas and with insufficiency of both exocrine and endocrine parts of the pancreatic gland.

A national prospective study in India showed that the most common etiology of chronic pancreatitis is idiopathic (60.2%) and alcohol related (38.7%) when compared to US where the most common etiology for chronic pancreatitis is alcohol.[77]

The pancreatitis has been classified by various classifications but the classifications which are utilized more commonly are two classifications **a.** TIGAR-O and **b.** M-ANNHEIM.[78,79]

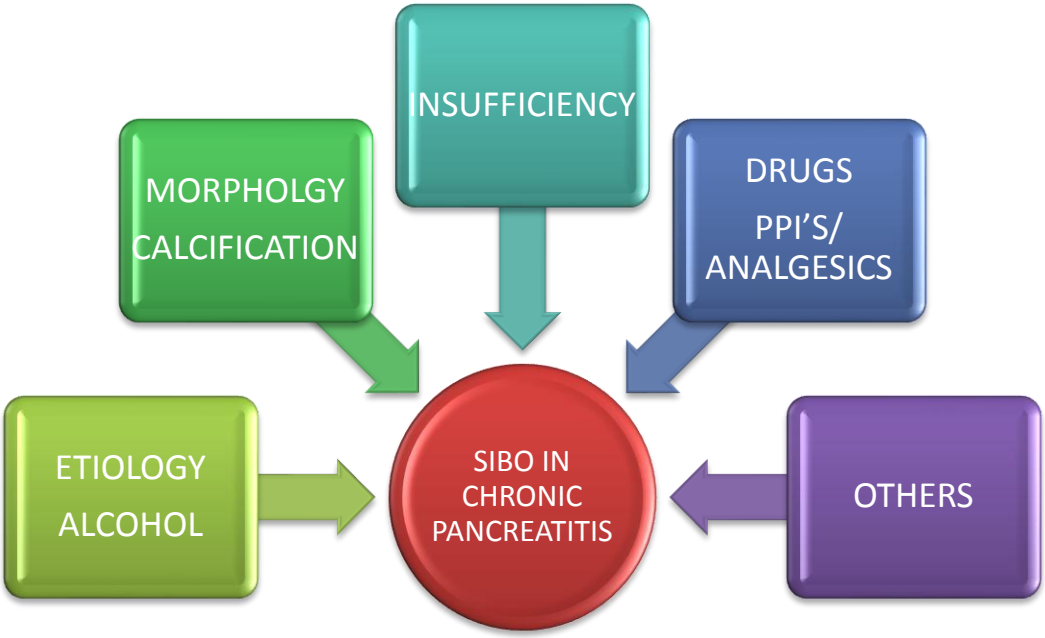
In the year 2007 Schneider A et al from Germany classified chronic pancreatitis as M-ANNHEIM (multiple risk factors – alcohol, nicotine, nutritional factors, hereditary, efferent duct factors, immunological and miscellaneous factors) which included the clinical stage (clinical symptomatic and asymptomatic stage), the etiology and severity of the disease (from clinical minor disease to exacerbated disease). They utilized a standardized scoring system which included the symptoms of pain and requirement of analgesics according to the WHO step ladder as well as imaging and treatment modalities opted for the management of chronic pancreatitis. Finally the chronic pancreatitis was graded according to the severity of the disease index and it had a range from minor to exacerbated disease index. A score was given which had a range from 0 to > 20 points.[80,79]

In the year 2001 Etemad et al had provided another classification of chronic pancreatitis named as TIGAR-O (toxic-metabolic, idiopathic, genetic, autoimmune, recurrent & acute severe pancreatitis and obstructive) which was based primarily upon the etiology of chronic pancreatitis. However this classification when compared to M-ANNHEIM, did not include the clinical symptoms, the management and prognosis of the disease depending upon the overall severity of the disease. However when compared to M-ANNHEIM classification, it was more simple and easily applicable to the clinical practice.[78]

Chronic pancreatitis and SIBO:

Etiology:

1. PPI (proton pump inhibitor) usage
2. Drugs :- Analgesics
3. Alcohol[14]
4. Gastric and pancreatic surgery
5. Advanced age
6. Pancreatic calcification[14]



SIBO is considered to be present in chronic pancreatitis patients, when they don't respond to the usual treatment and have malabsorption despite an adequate pancreatic enzyme replacement.

Trepsi et al in1999 showed that SIBO is more frequent in chronic pancreatitis and pancreatic insufficiency particularly who underwent gastroduodenal surgery. They used glucose hydrogen breath test for diagnosis of SIBO. However in this study a small group of patients with chronic pancreatitis were taken (n=35). The patients of chronic pancreatitis with exocrine insufficiency and gastroduodenal surgery were compared with patients with gastroduodenal surgery alone using a glucose hydrogen breath test. The study found that SIBO was seen in 34 % of patients with chronic pancreatitis and exocrine insufficiency when compared to control group which had GHBT positivity of 21 % only. The SIBO was more likely to be present if the etiology of chronic

pancreatitis was alcohol, there were associated pancreatic calcifications, there was associated gall stones and in patients who had a gastric resection. The study found that the diarrhoea was the only statistically significant factor in patients with chronic pancreatitis patients, when compared with the control group. The patients diagnosed with SIBO were given a non absorbable antibiotic rifaximin 400 mg thrice a day for one week every monthly.[14]

Mancilla et al also showed that the SIBO was more common in patients with chronic pancreatitis and may be the cause for persistent symptoms despite adequate treatment with pancreatic enzymes. This study used laculose hydrogen breath test for the diagnosis of SIBO. The study found that 92% patients with chronic pancreatitis had SIBO when compared to 7% in controls with a significant p value of <0.001. The study concluded that proper diagnosis and treatment of SIBO may help in improvement in symptoms and life .[81]

Lambacke et al in 1985 used 14C-cholylglycine breath test in patients with chronic pancreatitis and found that 40 % patients had SIBO. This may clinically manifest as diarrhoea and steatorrhoea, which may resolve after pancreatic enzyme supplementation.[83]

Grigoreva et al in the year 2010 established that SIBO is seen in majority of patients with chronic pancreatitits. The samples used in these patients were from the duodenum and found that there was association between duodenal inflammation, lymphangiectasia and SIBO with chronic pancreatitis.[84]

Bode et al in 2000 hypothesized that alcohol alone without chronic pancreatitis can lead to increased prevalence of SIBO and which may further may lead to malabsorption. The alcohol may interfere with local enzymes and can affect the absorption of macro and micro nutrients in the small bowel.[85]

Whereas Madsen et al in 2003 showed that SIBO may not be the factor leading to non tolerance of pancreatic enzyme supplementation in patients with chronic pancreatitis. They hypothesized that these patients can have altered small bowel permeability as well as bile acid absorption defect.[86]

RESULTS

Baseline demographics:

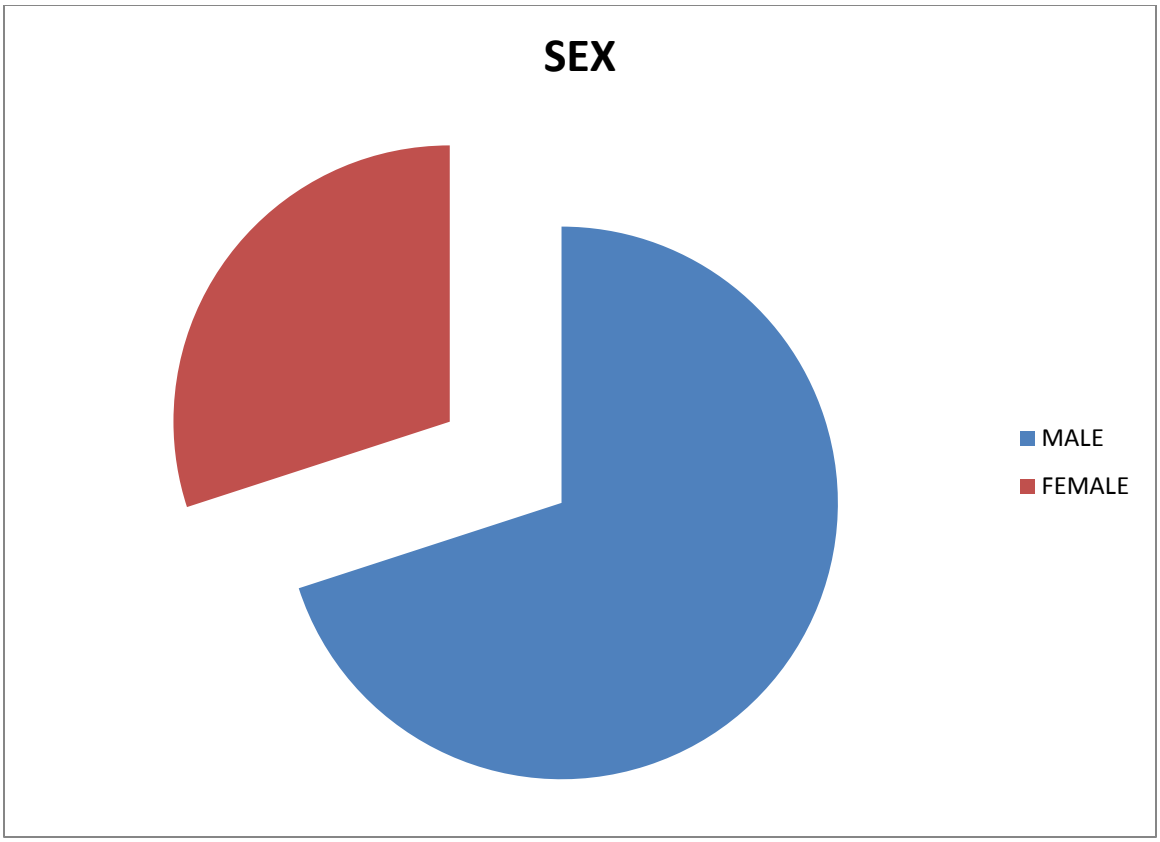
Of the consecutive 84 patients with a diagnosis of chronic pancreatitis who were initially screened, 36 were finally excluded from the final analysis

The patients who were not recruited for the study: 5 patients had pancreatic tumors,7 patients had failed jejunal intubation, 6 patient refused to give a consent, 8 patients did not undergo either of the two procedures- jejunal aspirate or glucose hydrogen breath test and 10 patients had taken drugs either a PPI or pancreatic enzyme supplementation prior to the procedure after the recruitment.

The consecutive 48 patients were included in the study.

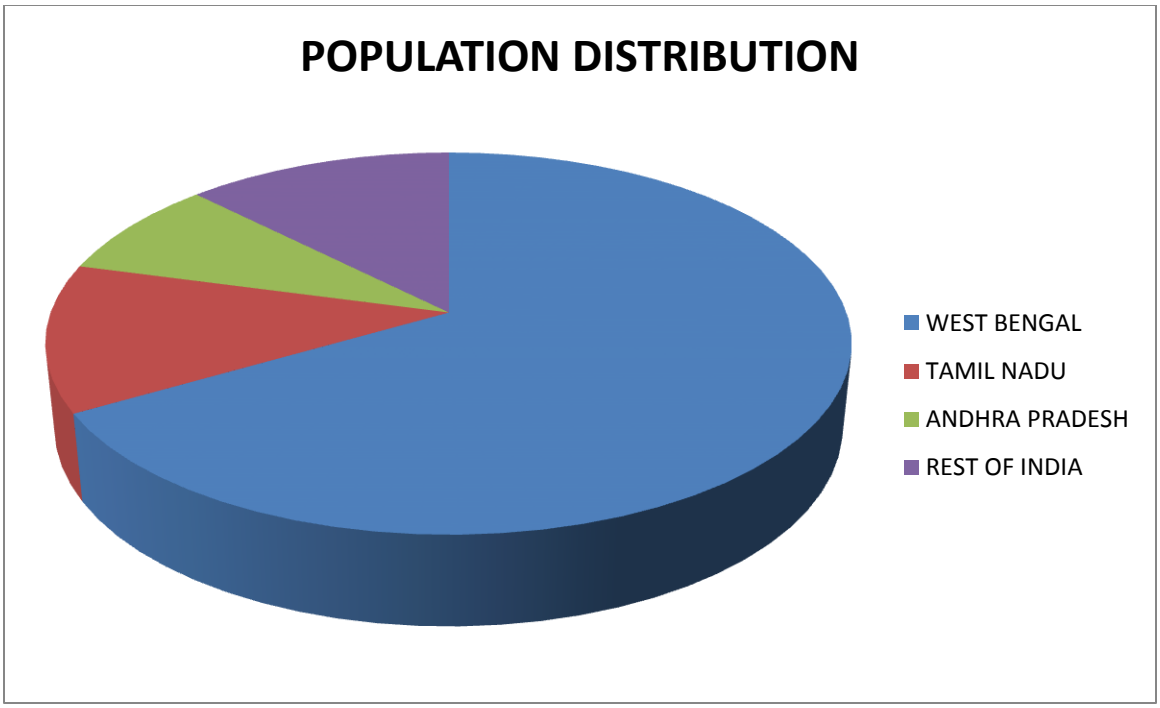
The duration of the study was from August 2011 to December 2012.

Of the 48 patients enrolled, majority were males 34/48(70%), as shown in the graph.



GRAPH 1: SHOWING SEX DISTRIBUTION

The patient distribution was majority from Eastern part of India followed by Tamil Nadu.



GRAPH 2: SHOWING THE POPULATION DISTRIBUTION

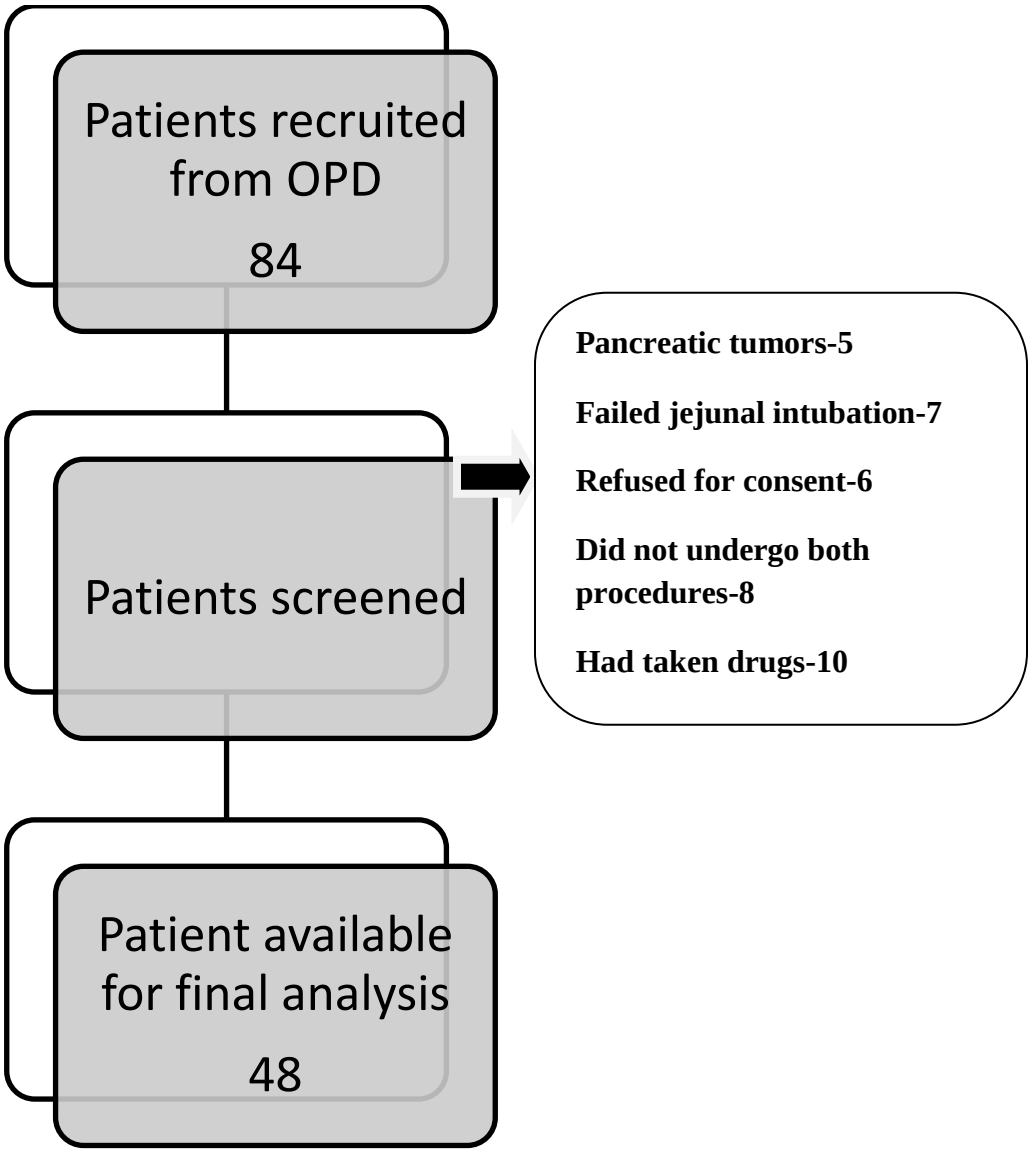
PATIENT CHARACTERISTICS

TABLE 3: SHOWING PATIENT CHARACTERISTICS

TOTAL PATIENTS	**n=48**
MALES	34
ALCOHOL (Etiology)	29
DIABETES MELLITUS	17
DYSPEPSIA	41
PAIN ABDOMEN	31
STEATORRHOEA (SYMPTOM)	18
BMI	19.2
HEMOGLOBIN	12.4 ± 1.6
ALBUMIN	4.5 ± 0.5
B_{12} (µg/dl)	Median 409
FOLIC ACID (pg/ml)	8.9 ± 4
STOOL FAT (72 HOUR)	24 patients
RADIOLOGICAL FINDINGS	
DILATED MPD	44
CALCIFICATIONS	38
PSEUDOCYST	15
VENOUS THROMBOSIS (PORTAL VEIN/ SPLENIC VEIN)	10
DILATED CBD / IHBRD	5

The mean age of the patients was 33.6 ± 10.4 years and the median age was 32.5 years.

All the study patients underwent the relevant clinical and laboratory evaluation as decided by the treating physician.



The etiology of chronic pancreatitis was idiopathic in majority 29/48 (60 %) followed by alcohol in 18/48 (37.5 %).

The most common presenting symptoms were dyspepsia and pain abdomen which were in 41/48(85 %) and 31/48(64 %) respectively.

The dyspepsia was present for a duration of 1-5 years in 34/41 patients.

The pain was present for 1-5 years in 21/31 patients with mild pain in 10 patients, moderate in 18 patients and severe pain in 6 patients respectively.

Steatorrhoea was the presenting complaint in 8/48 (16.6%) and it's total duration was less then 1 year.

The mean BMI of the patients was 19.2 and the socioeconomic status was low (modified Kuppuswamy scale).[15]

A total of 17 patients were on pancreatic enzyme supplements and 18 patients were on proton pump inhibitors prior to recruitment for the study. These patients were successfully able to stop the drugs for atleast 2 weeks and were recruited for the study.

The mean hemoglobin value was 12.4 ± 1.6 gm/ dl.

The mean serum albumin level was 4.5 ± 0.5 gm/ dl.

The most common diagnostic modality for diagnosis of chronic pancreatitis was CECT abdomen 43/48 (89 %) and two cases were diagnosed with EUS only.

The findings on the imaging were: dilated MPD (major pancreatic duct) was noted in 44/48 patients, the mean MPD diameter was 4.9 mm. The other most common findings were calcification (pancreatic parenchymal or intraductal) which was noted in 38/48 patients. The other findings were pseudocyst (15/48), venous thrombosis 10/48 (splenic vein thrombosis in 8/10 and portal vein thrombosis 2/10) respectively, CBD (common bile duct) dilatation and IHBRD (intrahepatic biliary radical dilatation) were noted in 5/48 patients respectively.

The mean 72 hour stool fat was 24 gm (n=34), although it could not be completed in 14 patients. Ten patients had pain abdomen after ingestion of fat for the test and the remaining four patients already had pain abdomen due to which the test could not be ordered.

None of the patients with or without SIBO had folic acid level > 20 pg/ml and the serum vitamin B_{12} levels were low as shown by previous studies.[59]

The mean B_{12} levels were 487.2 μg / dl and the median value was 409 μg/dl, with a range of 144 -1214 μg/dl.

The mean folic acid level was 8.9 ± 4 pg/ ml.

Average M-ANNHEIM score was between 6 –10(showing medium risk), with a mean of 7 in patients with SIBO and 6 in patients with non - SIBO respectively.

Jejunal aspirate:

The aspiration was done in all the patients and all the samples were cultured. The positive result was depicted by the growth of the colonies over the culture media and the serial dilutions required for each sample. Sixteen patients had growth of $> 10^5$ cfu / ml and were diagnosed as SIBO (small intestinal bacterial overgrowth).

There was mixture of organisms noted in 14 samples and the predominant organisms were aerobic with significant anaerobic organisms as well, as shown by the aerobic culture media.

In 9 patient samples the predominant organisms were anaerobic with significant aerobic bacteria as well. The rest of the 32 patients had growth but $< 10^5$ cfu / ml. The patient samples had mixture of both anaerobic and aerobic organisms with most dominant being the anaerobic bacteria.

Out of 32 patients with non SIBO (small intestinal bacterial overgrowth), 22 of them had bacterial CFU of $10^3 – 10^4$ / ml of the fluid. Two patients had CFU count $\leq 10^1$ and six patients had CFU $\leq 10^2$ / ml respectively.

TABLE 4: SHOWING COLONY FORM UNITS AND PATIENTS

COLONY FORMING UNIT / ML (CFU)	NO. OF PATIENTS
$\leq 10^1$	2
$\leq 10^2$	6
$\leq 10^3$	13
$\leq 10^4$	9
$\leq 10^5$	2
$> 10^5$	16

Glucose hydrogen breath test:

The glucose hydrogen breath test was used for diagnosis of SIBO in patients of chronic pancreatitis.

The technique was defined earlier in the methodology.

The machine used was Bedfont, from UK and the amount of glucose given was 50 gram dissolved in 250 ml of fresh water.

Breath samples of all the 48 patients were collected and result was generated in form of a graph and a table along with the graph. The results were reported as glucose intolerant or negative for intolerance.

Out of 48 patients 12 had glucose intolerance on breath testing. When compared to the jejunal aspirate two patients were false positive, ten were true positive and six was false negative.

The median breath hydrogen level was 16.5 ppm in SIBO (small intestinal bacterial overgrowth) with a range of 4-41 ppm whereas in non-SIBO (small intestinal bacterial overgrowth) the median breath hydrogen level was 5.25 ppm with a range from 1-26 ppm respectively.

Patients with SIBO (small intestinal bacterial overgrowth):

A total of 16 patients had SIBO (small intestinal bacterial overgrowth) with a CFU count in jejunal aspirate of $> 10^5$/ml.

Out of 16 patients 12 were males and 4 were females, all females with diabetes had SIBO (small intestinal bacterial overgrowth).

10 patients with steatorrhoea had SIBO (small intestinal bacterial overgrowth).

The dyspepsia was more common in patients without SIBO, however it was non significant.

The pain as symptom was more common in patients with SIBO, it was non significant.

The 24 hour stool fat was more common in patients with SIBO (62%) but it was non significant.

When imaging findings were compared between SIBO and no-SIBO, the calcification was more common in patients with SIBO (62%). The pseudocyst was seen slightly more common in SIBO (37%) versus non-SIBO (31%).

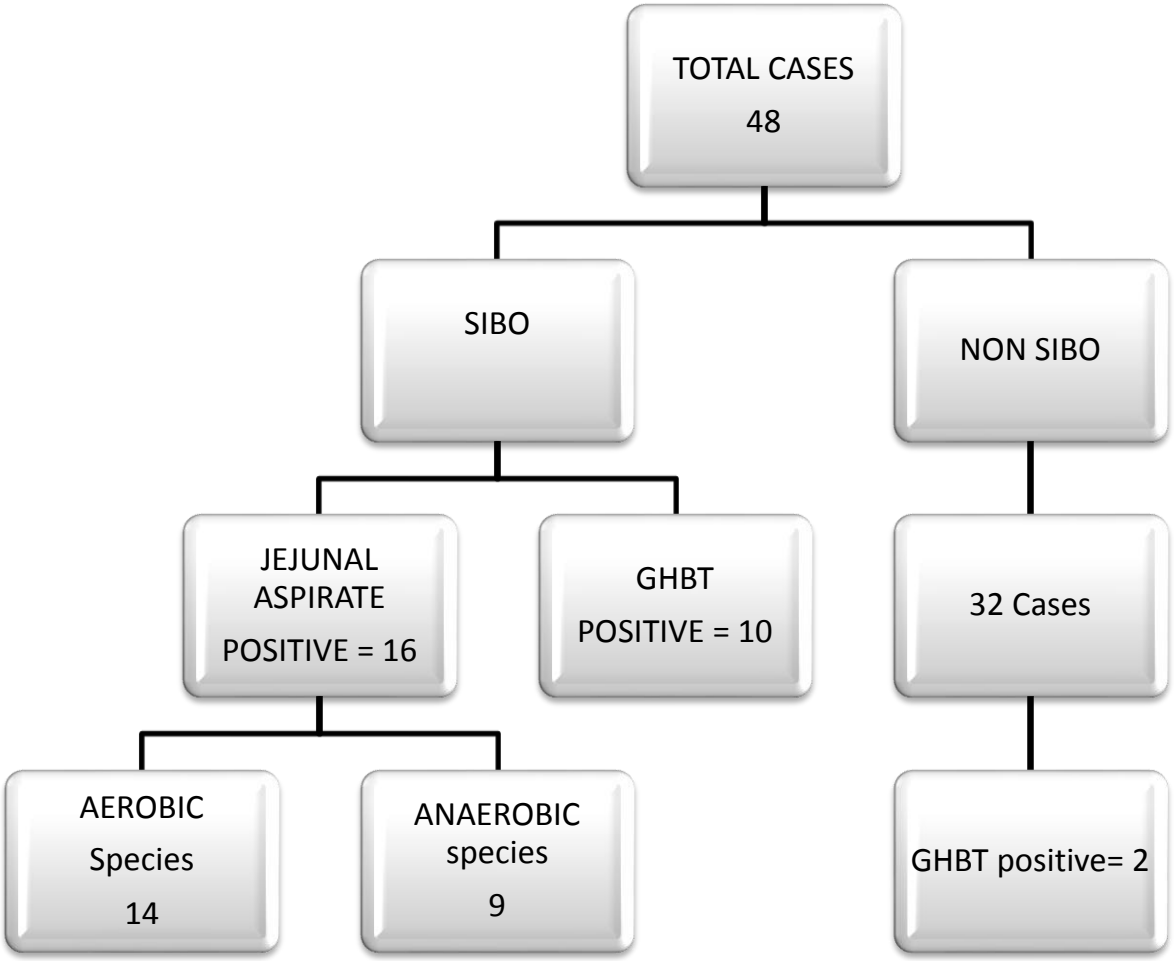
The venous thrombosis was also seen slightly more common in patients with SIBO (25%) versus non-SIBO (18.6%).

The median GHBT level was 16.5 ppm and 5.25 ppm in SIBO and non-SIBO respectively. The range of GHBT was 4-41 ppm and1-26 ppm in SIBO and non-SIBO respectively.

The GHBT values were significant when compared between SIBO and non-SIBO, the p value was <0.001.

TABLE 5: SHOWING CHARACTERISTICS OF PATIENTS WITH SIBO AND NON SIBO

Characteristics of patients	**NON SIBO**	**SIBO**	**p VALUE**
PATIENTS	32	16	-
SEX DISTRIBUTION (MALE/ FEMALE)	24 / 8	12 / 4	NS
ETIOLOGY (ALCOHOL/ NON ALCOHOL)	12 / 20	6 / 10	NS
DIABETES (PRESENT/ ABSENT)	13 / 32	4 / 16	0.35
DYSPEPSIA (PRESENT/ ABSENT)	28 / 32	13 / 16	0.45
PAIN (PRESENT/ ABSENT)	18 / 32	13 / 16	0.12
STOOL FAT (PRESENT/ABSENT)	8 / 32	10 / 16	NS
IMAGING FINDINGS			
CALCIFICATION	12/32	10/16	0.13
PSEUDOCYST	10/ 32	6/ 16	0.67
VENOUS THROMBOSIS(SVT/PVT)	6/ 32	4/ 16	NS
GHBT	2	10	NS
MEDIAN LEVEL (ppm)	5.25	16.5	< 0.001
M-ANNHEIM	6	7	NS


TOTAL CASES
48
SIBO
NON SIBO
JEJUNAL ASPIRATE
POSITIVE = 16
GHBT
POSITIVE = 10
32 Cases
AEROBIC
Species
14
ANAEROBIC
species
9
GHBT positive= 2

DISCUSSION

Our study was aimed to find out the frequency of SIBO in chronic pancreatitis and also to find whether GHBT can be used to diagnose SIBO.

Clinical and investigation profile of chronic pancreatitis patients was done and these were later on studied to find any difference between the SIBO and non-SIBO patients in the final analysis.

It was a pilot study and only study group was included, there was no control group, as it was not approved by the institutional review board.

The most common etiology for chronic pancreatitis was idiopathic as shown by the national survey done for etiology of chronic pancreatitis.[77]

SIBO was found in 1/3rd patients with chronic pancreatitis. This is comparable with the literature available.

There could be multiple factors which may lead to SIBO in chronic pancreatitis such as

1. Due to decreased pancreatic enzymes especially lipase which may lead to loss of inhibition of growth of bacteria which leads to their overproduction.
2. The other factor may be use of PPI's in all most of these patients which may lead to decreased gastric acid production.
3. The use of analgesics especially opioids may lead to altered motility and stasis which leads to bacterial overgrowth.

4. The patients with gastroduodenal surgery in chronic pancreatitis also have increased incidence of SIBO which could be due to altered anatomy, which we did not included in our study.
5. The advanced age and achlorhydria may predispose to SIBO due to loss of gastric acid action on the growth of the bacteria.

The strength of our study was that, we utilized the gold standard for diagnosing SIBO (jejunal aspirate).

Our study is the 1st study published in English literature to use gold standard for diagnosing SIBO in chronic pancreatitis. All the previous studies have utilized breath tests for diagnosis of SIBO in chronic pancreatitis.

The mean age of the patients was 42 years and predominant patients were males comprising more than 2/3rd. Most patients came from East and South India reflecting the patient population visiting CMC.

Dyspepsia and abdominal pain were the most common presenting symptoms. Dyspepsia was more common in the non-SIBO patients whereas pain was more common in the SIBO patients respectively, however none of them was statistically significant.

Mean Hemoglobin and albumin were comparable between the two groups and for the whole study as well.

Alcohol was the most common etiology and there was no difference in etiology between SIBO and non-SIBO. The increased incidence of SIBO among the alcoholics may be due to altered small bowel permeability, altered mucosal enzymes and altered small bowel motility.

Diabetes mellitus was present in similar number between the two group of patients and all female diabetics were having SIBO. The onset of diabetes in chronic pancreatitis signifies advanced disease and more chances of developing SIBO.

The 72 hour stool fat value was higher in SIBO patients and more patients with SIBO had steatorrhoea. But it was statistically non significant. The presence of steatorrhoea in chronic pancreatitis represents advanced disease with severe organ insufficiency which may lead to SIBO.

The imaging diagnosis of chronic pancreatitis was done with CT abdomen in majority of patients and some findings were seen more in patients with SIBO such as pancreatic calcifications (parenchymal and ductal) and venous thrombosis (portal and splenic). This was also shown by Trepsi et al in 1999 that the prevalence of SIBO was higher in patients with chronic pancreatitis and there was increased association with alcohol abuse, microclacifications of pancreas, cholelithiasis, diabetes and diarrhea. Where as in our study, we found that alcohol abuse and

pancreatic calcification were more common in patients with SIBO but these were statistically nonsignificant when compared with non SIBO patients. The increased frequency or pancreatic calcifications and venous thrombosis in our study was associated with SIBO, which may be due to advanced and severe disease.

The median M-ANNHEIM score was higher in SIBO than non SIBO but it was statistically non significant. In a recent study done in 2012, the M-ANNHEIM score in chronic pancreatitis was 5.[10]

In our study we used GHBT in addition to jejunal aspirate in patients with SIBO and we tried to find the sensitivity and specificity of GHBT. We completed GHBT in all patients who were recruited in the study. The median level of hydrogen in the breath was higher in SIBO patients and it was significant with a $p < 0.0001$. Ten patients who had SIBO diagnosed by jejunal aspirate were glucose intolerant and were correctly diagnosed by the GHBT. In six patients the GHBT was negative, which could be attributed to the patients being methane producers. As shown in literature that 15 % of patients may be methane producers and will be negative on GHBT .

In two patients the GHBT was false positive and it could be related to patient factors

a. Due to intake of fiber or fermentative diet in previous night prior to the GHBT

b. Oral Bacteria which could be due to improper mouth gargle and poor oro dental hygiene. Although it was mandatory for all patients to avoid taking high dose carbohydrates and do a good mouth gargle with a disinfectant prior to giving a breath sample.

The sensitivity of the GHBT was 62% and the specificity was 92% which is comparable to other studies published in literature, comparing GHBT and jejunal aspirate. Although none of them has compared GHBT and jejunal aspirate in chronic pancreatitis. [45,60,61,62,63,64]

As the table 6 shows that the number of patients recruited in these studies is small and comparable to our study. Only one study by Corraza et al had patient numbers more than our study. They utilized both lactulose and GHBT for diagnosis of SIBO in malabsorption syndrome. They compared the breath tests with culture and found the sensitivity and specificity of both tests was 62%, 68% and 83%, 84% respectively.

A similar study was done by Ghoshal et al in 2006 from India and it showed that in a small number of patients, the sensitivity of the GHBT was 45% and the specificity was 80 % respectively, these results were comparable to our study. However our results showed a higher sensitivity and specificity, this could be due to more strict inclusion and exclusion criteria. For e.g any patient who was unsure about the intake of antibiotics in last 3 months was excluded and patient with intake of PPI's and pancreatic enzyme supplementation. The reason may be due to a small study group of 48 patients.

TABLE 6 : SHOWING THE COMPARISON BETWEEN OUR STUDY AND PREVIOUS STUDIES

Author	No of patients	Test	Gold standard	Sensitivity	Specificity
Our study	48	GHBT	Culture	62%	89%
Bauer[60]	40	GHBT	CULTURE	41	80
DONALD[61]	39	GHBT/ BABT/ XBT	CULTURE	20/30/33	77/89/76
CORAZZA[62]	77	GHBT/ LBT	CULTURE	62/68	83/44
KERLIN[63]	27	GHBT/ RICE BREATH TEST	CULTURE	93/ 81	78/ 67
GHOSHAL[45]	32	GHBT / LBT	CULTURE	45 /31	80/ 86
MAC MOHAN[64]	30	GHBT	CULTURE	75	30

GHBT= Glucose hydrogen breath test, BABT= Bile acid breath test, XBT= Xylose breath test and LBT= Lactulose breath test

Thus SIBO is not uncommon in chronic pancreatitis and seen in 1/3rd of patients. GHBT can be used for diagnosis of SIBO in these patients.

CONCLUSION

1. SIBO was not uncommon in patients with chronic pancreatitis.
2. SIBO was diagnosed in 1/3rd of patients with chronic pancreatitis.
3. GHBT can be used for diagnosis of SIBO and with a sensitivity of 62% and a specificity of 92% respectively.

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STUDY NUMBER:

PROFORMA FOR CHRONIC PANCREATITIS

NAME	AGE	SEX	OCCUPATION

RESIDENCE	BMI	SOCIOECONOMIC STATUS	

ALCOHOL/ NON ALCOHOL

DIABETIC/ NON DIABETIC

SYMPTOMS

DYSPEPSIA	PAIN	BLOATING	REFLUX	

SIGNS

MALNUTRITION	ABDOMINAL MASS	SYSTEMIC FINDINGS	MISC

SCORE:

LABS AND OTHER INVESTIGATIONS

BLOOD: CBC

LFT

OTHERS

PANCREATITIS WORK UP

IMAGING: TYPE OF STUDY – CECT ABDOMEN/ US ABDOMEN

MPD	
GLAND	
PARENCHYMA	
CAVITY	
HEAD/BODY	
COMPLICATIONS	

BLOOD: VITAMIN B 12/FA -

VITAMIN D -

72 HR STOOL FAT:

EUS / ERCP:

SCORE:

GLUCOSE HYDROGEN BREATH TEST

0 MIN	15	30	45	60	75	90	120	150	180

JEJUNAL ASPIRATE

	ORGANISMS	
	AEROBIC	ANAEROBIC
CFU		

S. No	Name	Age	Sex	MRD	BMI	SES	RESI	OCC	ETIOLOGY	DIABETES	FAMILY	PAIN
1	pr	28	m		15.6	low	wb	mech	alc	diab	nil	occ
2	bs	48	f		22	low	wb	hw	na	diab	nil	mod
3	lkb	45	m		21	low	wb	lab	alc	non	nil	sev
4	d.r	20	f		20.8	mid	tn	nur	na	non	nil	occ
5	hm	36	m		16.4	low	ban	lab	na	non	nil	sev
6	ss	40	m		15	low	wb	far	alc	diab	nil	sev
7	sk	26	f		23.4	low	wb	hw	na	non	nil	mod
8	sm	25	m		23	low	wb	far	na	non	nil	occ
9	br	49	f		19	low	tn	hw	na	diab	nil	occ
10	mmq	36	m		18	mid	ban	pvt	na	diab	nil	occ
11	ab	28	m		16	low		pvt	na	diab	nil	occ
12	emr	30	m		17.8	low	ban	far	na	diab	nil	occ
13	rcb	30	m		21	mid	wb	pvt	na	non	nil	occ
14	vm	35	m		21	low	ap	lab	alc	non	nil	occ
15	mg	42	m		20.1	low	wb	lab	alc	non	nil	occ
16	vr	40	m		21.7	upp	tn	en	alc	diab	nil	occ
17	ac	20	m		21	mid	wb	stu	na	non	nil	mod
18	BKD	26	M		20	low	wb	pvt	na	diab	nil	NIL
19	mm	28	m		19	low	wb	lab	na	non	nil	
20	uk	28	f		22	low	tn	u	na	diab	nil	occ
21	nn	27	f		21	low	ap	pvt	na	non	nil	mod
22	ks	33	f		22	mid	wb	hw	na	diab	nil	mild
23	mzh	40	m		19.5	mid	ban	g	na	non	nil	mild
24	bd	21	m		15.6	low	wb	far	na	non	nil	occ
25	ns	28	m		18.7	mid	ap	pvt	na	non	nil	mod
26	rd	40	m		19	low	tn	lab	na	non	nil	occ
27	ckm	35	m		18.9	low	wb	pvt	alc	non	nil	occ
28	ak	35	f		16	mid	wb	pvt	na	non	nil	occ
29	aan	47	m		23	mid	tn	govt	alc	non	nil	NIL
30	sna	24	m		17.5	low	wb	pvt	na	non	nil	occ
31	snd	45	m		18.3	mid	wb	pvt	alc	non	nil	NIL
32	ra	21	m		16.5	low	wb	stu	na	non	nil	occ
33	knp	32	m		21	low	wb	lab	na	non	nil	mild
34	kal	21	f		15.6	low	tn	hw	na	non	nil	mod
35	sm	35	m		20	low	wb	lab	alc	non	nil	occ
36	sd	55	m		23	low	chg	lab	alc	diab	nil	mod
37	sk	23	m		24	low	wb	lab	na	non	nil	NIL
38	kkn	55	m		21	low	nep	retir	na	diab	nil	mild
39	ask	25	f		20	low	wb	hw	na	diab	nil	mild
40	skd	34	m		21	low	wb	lab	alc	non	nil	mod
41	mm	45	m		21	low	wb	lab	alc	non	nil	mod
42	sum	18	f		22	low	wb	stu	na	diab	nil	mild
43	dbp	45	m		21	low	chg	lab	alc	non	nil	mild
44	as.ch	54	m		22	low	wb	bus	alc	non	nil	NIL
45	kjm	43	m		23	low	ban	bus	na	diab	nil	NIL
46	ckm	26	m		21	low	wb	lab	na	non	nil	NIL

47	anb	23	m	19	low	wb	lab	na	diab	nil	NIL
48	shu.s	19	m	17	low	wb	stu	na	non	nil	NIL

DYSPEPSIA	STEATOR	MALNUTR	Hb	ALBUMIN	SAP	B12	FA	STOOL	IMAGING	GHBT	JEJ ASP
pos	neg		13	4.9	132	1214	10	55	4	neg	neg
pos	neg	nil	12	4.9	97			25	3	pos	pos
pos	neg	nil	13	5	83	450	7.5	26	4	neg	neg
pos	neg	nil	12	4.7	66	156	7.5	19.6	3	neg	neg
pos	pos	pos	10	3.6	306	448	6.1	24	3	pos	pos
pos	neg	pos	12	4.4	284	364	13	nd	3	neg	neg
pos	neg	nil	12	4.7	91	566	8.6	15	2	neg	neg
pos	neg	nil	13	5	27	622	8.7	23	eus	neg	neg
pos	neg	pos	11	3.9		1074	10	63	2	pos	neg
pos	pos	nil	13	4.7	92			16	4	neg	neg
pos	neg	pos	9.7	4.6	139	370	15	32.2	4	neg	neg
pos	pos	nil	11	4.2	169			32.6	3	neg	neg
pos	neg	nil	12	4	140	322	9.3	nd	1	neg	neg
pos	neg	nil	14	4.8	206			29.4	4	pos	pos
pos	neg	pos	11	4.1	69	331	7.4	nd	4	neg	neg
pos	neg	nil	13	4.7	61	466	4.2	11.3	4	neg	neg
pos	neg	nil	15	5	75	263	5	11	2	neg	neg
pos	neg	nil				241	5		3	neg	neg
			14	5	104			11.2	2	pos	pos
pos	neg	nil	12	4.6		313	4.4	12	2	neg	pos
pos	neg	nil	7			929	4	14	3	pos	pos
pos	neg	nil				1030	19	11	3	neg	pos
pos	neg	pos	12	4.6		296	7		2	neg	neg
n	neg	pos	15	4.9		161	6	16.7	4	pos	pos
pos	neg	pos	14	5		144	3.6	nd	3	neg	pos
neg	neg	nil	13	4.5	512	512	11	nd	2	neg	neg
pos	neg	pos	13	4.6	57	674	8	25	2	neg	neg
pos	neg	pos	13	4.3		233	10	20.6	2	neg	neg
pos	neg	nil	14	4.5	312	312	5	nd	1	neg	pos
pos	neg	pos	11	5		1096	10	nd	2	pos	pos
neg	pos	pos	11	4.7	52	306	10	66.9	3	neg	neg
pos	neg	pos	13	4.9		235	9.7	23	2	neg	neg
pos	neg	nil	13	4.5	65	169	5.6	12.3	2	neg	neg
pos	neg	nil	13	4	88	317	5	21	3	neg	neg
pos	neg	nil	13	4		212	14	23.6	5	neg	neg
pos	pos	pos	11	3.2	64	560	13	21	4	neg	neg
neg	neg	nil	13	4.8	94	731	5.1		5	pos	neg
pos	neg	pos	13	3.8	79	714	14	79.7	5	neg	neg
pos	neg	nil	13	4.8	88	463	9	52.4	6	pos	pos
pos	neg	pos	13	4.9	92	290	6.8		5	pos	neg
pos	neg	nil	13	5	107	654	17	23	5	pos	pos
pos	neg	nil	12	4	147	481	9.8	22	5	neg	neg
pos	neg	nil								neg	neg
pos	neg	nil	14	5		335	5.2	23	4	neg	neg
pos	neg		13	5	99	999	20	58	5	neg	neg
pos	neg	nil	15	4	60	653	10	23		neg	pos

pos	neg	nil	13	4	61	674	7.9	23	6	neg	pos
pos	pos	nil	8	3	89	221	5.6		5	pos	pos